UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	11

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/247,874	Applicant(s) Duff
	Examiner Richard Schnizer	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Jul 3, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-14 and 34-44* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14 and 34-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *16*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

An amendment was received and entered as Paper No. 9 on 7/3/00. Claims 40 and 41 have been canceled as requested. Applicant requested replacement of Fig. 2 with an amended version. Unfortunately, the amended version was apparently omitted or lost, and has not been entered. Applicant is reminded that any proposal to amend a drawing must be embodied in a separate letter to the Draftsperson. See MPEP 608.02(r).

Election/Restrictions

Applicant's election of group I, claims 1-14 and 37-42, in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 15-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-14, 35, 36, 43, and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14, 43, and 44 are directed to methods and kits the use of which depend on the sequence of the IL-1B allele (+6912). Claims 35 and 36 are drawn to nucleic acids of SEQ ID NO:2 which comprise a cytosine at position 6912. The sequence of IL-1B allele 2 (+6912) was initially disclosed as one in which the nucleotide at position 6912 was a G residue. The specification was subsequently amended to redefine this allele as comprising a C residue at position 6912. Applicant initially disclosed a polynucleotide sequence in Fig. 1 which was referred to as the sequence of human IL-1B GEN XO4500, as well as a polynucleotide sequence in Fig. 2 which was referred to as the IL-1B allele 2 (+6912). These sequences both comprised a G residue at position 6912. In the Sequence Listing supplied by applicant, position 6912 is a T residue in both SEQ ID NO:1 and SEQ ID NO:2. Positions 8845 of SEQ ID NO:1 and SEQ ID NO:2 appear to correspond to position 6912 of Figures 1 and 2. This position is a G in both SEQ ID NO:1 and SEQ ID NO:2. Because there appears to be no support in the specification as filed for a C residue at position 6912 of Fig. 1, Fig. 2, SEQ ID NO:1, or SEQ ID NO:2, nor at position 8845 of SEQ ID NO:1 or SEQ ID NO:2, the claims as amended recite new matter.

In order to overcome this rejection, Applicants must establish that, at the time of filing, they were in possession of the claimed invention, *i.e.* a polynucleotide identical to that disclosed in Figure 1, except that it comprises a C rather than a G at position 6912. Furthermore Applicants must establish that the IL-1B sequence comprising a G residue at position 6912 (human IL-1B GEN XO4500) was recognized in the prior art as the wild type sequence, and that the nucleic acid of the instant invention is, in fact, not wild type.

Written Description

Claims 42 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record in Paper No. 8.

Claims 42 is a method claim which is drawn to the genus of transgenic non-human animals comprising SEQ ID NO:2 and a phenotype characteristic of inflammatory disease. The specification fails to adequately describe a number of species of the genus of transgenic non-human animals which is sufficient to convey to one of skill in the art that Applicant was in possession of the claimed invention at the time of filing.

Response to Arguments

Applicant's arguments filed 7/3/00 have been fully considered but they are not persuasive. Applicant argues that the specification and claims disclose many relevant identifying characteristics, and that these are sufficient to justify a claim to the genus of transgenic non-human animals comprising SEQ ID NO:2 and a phenotype characteristic of inflammatory disease. Specifically, applicant argues that the recitation of the characteristics "non-human" and "contains and expresses an isolated nucleic acid of SEQ ID NO:2" provide a sufficient description to convey possession of the invention.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440. The guidelines state that, for genus claims, a representative number of species must be described, and this description may take the form of a disclosure of relevant identifying characteristics. The guidelines further define a "representative number".

> " What constitutes a representative number is an inverse function of the level of knowledge and skill in the art. Satisfactory disclosure of a representative number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, written description of a genus which embraces widely variant species cannot be achieved by disclosing one species within the genus."

In this case the claim encompasses widely variant species including any and all animals which have an inflammatory disorder caused by expression of a transgene comprising the nucleic acid of SEQ ID NO:2. It is well known in the art that the phenotypes of transgenic animals are highly unpredictable. As pointed out by Applicant, the prior art shows that expression of human IL-1B

in mice alone results in a wide variety of phenotypes. Extrapolation of these phenotypes to such diverse animals as lobsters, whales, and spiders, all of which are encompassed by the claim, cannot be performed with confidence by one of skill in the art. In addition, Applicant fails to disclose a single example of any species of the claimed genus with any phenotype. Because of the unpredictable nature of the art, a broad description of the identifying characteristics of the species, in the absence of any example, is insufficient to convey possession of the invention.

Enablement

Claims 1-14, 37-39, and 42 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record in Paper No. 8 unless such reasons are specifically withdrawn below.

With respect to claims 1-14, the invention comprises methods of determining susceptibility to diseases or conditions which are caused by high levels of IL-1β, and kits for performing the methods. The methods depend on detection of a recently discovered genetic polymorphism in the IL-1β gene (IL-1B) which is associated with chronic overproduction of IL-1β. The polymorphic marker is called IL-1B allele 2 (+6912).

The disclosure fails to enable the claimed invention because it does not provide convincing biochemical evidence which links the overexpression of IL-1B to any disease, and because no such evidence is present the prior art.

Response to Arguments

Applicant's arguments filed 7/3/00 have been fully considered but they are not persuasive.

The specification establishes a correlation between several diseases and a specific haplotype (33221461) which comprises several alleles of the IL-1 gene cluster including IL-1B. The prior art teaches that identification of this haplotype should "allow the investigator to begin to determine which of the alleles are causative, rather than merely linked to a disease-causing allele". See page 13, lines 16-18 of WO 98/54359. Thus at the time of the invention, no biochemical linkage between IL-1β overexpression and any disease state had been established. Applicant asserts that a point mutation in the 3'UTR of the IL-1B gene causes overexpression of IL-1B. See page 10, lines 9-12. This represents an initial step towards identifying the disease-causing allele, but does not provide convincing evidence that excludes any of the other alleles of the haplotype. Applicant suggests that additional biochemical experimentation is unlikely to provide additional evidence of linkage between overexpression of IL-1B and a disease state, particularly because biochemical experimentation must be performed *in vitro*. Further steps which would strengthen the case for the mutated IL-1B allele include demonstrating that the expression of the other alleles of the haplotype occurs in response to known stimuli similarly to those of haplotypes not associated with disease, and demonstrating that the other alleles of the haplotype

encode polypeptides which function normally. Such steps are well within the ability of one of skill in the art. Elimination of the other alleles in the haplotype as potential causes would be considered logical and routine in establishing a causal link between one member of the haplotype and any disease. The rejection is maintained.

The arguments with respect to a lack of enablement due to improper incorporation of essential material are withdrawn.

With respect to claims 37-39 and 42, the invention encompasses transgenic non-human animals of any species which contain and express SEQ ID NO:2. The transgene may be expressed in any quantity. The animals of claims 37-39 are not characterized by any phenotype which distinguishes it from any other animal. The specification does not teach how to use a transgenic animal which lacks a distinguishing phenotype. The animal of claim 42 comprises a phenotype characteristic of an inflammatory disorder. The specification does not teach how to make an animal with any specific phenotype including an inflammatory disorder.

Response to Arguments

Applicant's arguments filed 7/3/00 have been fully considered but they are not persuasive. Applicant argues that the phenotype of transgenic mice comprising a human IL-1B allele is known in the art, and relies on Lai for support.

Lai teaches a mouse containing a transgene comprising sequences encoding mature IL-1B, fused to a the human TPA secretion signal and the bovine growth hormone polyadenylation signal. Transcription is under the control of the alpha crystalline promoter and is restricted to the eye. As is well known in the art, the phenotype of a transgenic animal is dependent on the expression of the transgene. In this particular case, at least three expression control elements can be considered to contribute to the phenotype of the mouse. None of these transcription control elements is contained within SEQ ID NO:2, nor is any one of them disclosed in the instant specification. It is not reasonable to assume that one would arrive at the phenotype of Lai by constructing a transgenic mouse which expresses the entire sequence of SEQ ID NO:2, as required by the claim. SEQ ID NO:2 comprises 1933 bases of normally untranscribed sequence upstream of the normal IL-1B transcription start site. It seems highly unlikely that operable linkage of these sequences to a heterologous promoter would result in the expression of IL-1B. This is because there are start codons in each reading frame at positions -1136, -1369, and -1422, as well as stop codons in each reading frame at positions -670, -665, and -597. It is likely that this arrangement would preclude translation of IL-1B from an mRNA produced from a heterologous promoter linked to SEQ ID NO:2. However, even if these start codons were not recognized, the addition of at least 1933 bases on the 5' end of the message would have an entirely unpredictable effect on message stability and translation initiation. One of skill in the art could not expect to produce a transgenic mouse with any predictable phenotype using such a construct. If, on the other hand, transcription was driven by the IL-1B promoter, which is not

disclosed in the specification but is assumedly somewhere in the 1933 untranscribed bases of SEQ ID NO:2, then the phenotype of Lai would not be expected because expression should not be restricted to the eye, and the quantity of expression would not be expected to be the same as that achieved by Lai because of the different promoter, poly-addition, and signal sequences used. Applicant has not taught how to predict the activity of the human Il-1B promoter in non-human animals sufficiently well to predict the phenotype of those animals, and has not pointed to any evidence that such predictions can be made reliably by those of skill in the art. Furthermore, the mouse of Lai is rare in that it comprises only a single transgene copy, whereas most transgenic animals comprise multiple copies of inserted transgenes. Lai points out that the presence of only a single copy is likely to be the reason that the mouse was viable, because all other attempts to generate another transgenic line failed. See page 290, column 1, lines 4-12. Thus, the production of a transgenic animal comprising a human IL-1B gene appears to be unpredictable, and may be dependent on the number of copies of the transgene which are delivered. Applicant has not taught how to limit the number of IL-1B transgenes which are integrated into the host genome, and thus provides no guidance to overcome the unpredictability of making a mouse transgenic for IL-1B, much less the unpredictability of making any and all other transgenic animals.

Applicant also argues that in order to serve as a screening system for IL-1B agonists or antagonists a transgenic animal need only have a measurable phenotype that is dependent on the IL-1B gene. This may be true, but if that phenotype is not readily predictable or disclosed in the specification, then one cannot use the animal for anything. The phenotype of the claimed animals

is totally unpredictable because there is no way of knowing in advance how much IL-1B will be expressed in any cell of any transgenic animal, and even if there was a way, the effects of that expression on the animal itself are entirely unpredictable. Furthermore, as discussed above it is not clear that an animal which expresses the sequence of SEQ ID NO:2 will express any IL-1B at all. In order to teach how to use the claimed animal, the phenotype of that animal must be disclosed. Applicant has not disclosed the phenotype of any single transgenic animal, and has not established that any single claimed transgenic animal will even have a specific phenotype which would distinguish it from the wild type. Therefore the rejection is maintained as proper.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35 and 36 are indefinite because the meaning of the phrase "a cytosine at a position equivalent, relative to the surrounding sequence, to position 6912", is unclear. In particular, the phrase "relative to the surrounding sequence" renders the claim indefinite. This phrase implies that there is a reference base, or bases, in the surrounding sequence which is 6911 bases from position 6912. This is clearly impossible in molecules less than 6912 nucleotides in length. Also,

the failure to designate a single reference base means that there is no single position 6912. It appears that Applicant's intent is to refer to position 6912 of the nucleotide sequence of Fig.2. Applicant should bear in mind that the numbering of Fig. 2 is not equivalent to the numbering of SEQ ID NO:2, *i.e.* SEQ ID NO:2 begins with nucleotide number 1, whereas Fig. 2 begins with nucleotide -1933. Thus it appears that base 8845 of SEQ ID NO:2 corresponds to base 6912 of Fig. 2. Applicant should consider redrafting the claim such that it is drawn to an isolated nucleic acid comprised of between 100 and 7000 bases of SEQ ID NO:2, but which comprises a cytosine rather than a guanine at a position corresponding to position 8845 of SEQ ID NO:2. It is noted that such a claim would still constitute new matter if Applicant fails to overcome the new matter rejection outlined above. Applicant should also check the examiner's arithmetic with regard to defining position 8845.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34 stands rejected under 35 U.S.C. 102(b) as being anticipated by Clark et al (GenBank Accession No. X04500).

Clark teaches a genomic sequence for human prointerleukin 1 beta which is 100% identical to the sequence of SEQ ID NO:2. See sequence alignment enclosed in Paper No. 8. Thus Clark anticipates the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 35 stands rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Clark et al (Nuc. Acids Res. 14(20): 7897-7914, 1986) and Clark et al (GenBank Accession No. X04500, 6/1997).

Clark (1997) teaches a genomic sequence for human prointerleukin 1 beta which is 100% identical to the sequence of SEQ ID NO:2. The sequence of nucleotides in this molecule was determined by Sanger sequencing (See Clark (1986) page 7899, first full paragraph). One of skill in the art appreciates that this technique produces a variety of nucleic acid molecules which differ in length by a single base. These molecules are separated from each other by polyacrylamide gel electrophoresis. It is well known to one of skill in the art that, at the time of the invention, a standard sequencing gel easily resolved fragments of 100 to 200 nucleotides. Thus, on the sequencing gel in which the G residue was resolved at position 6912, there must have been

polynucleotides in excess of 100 nucleotides in length which comprised the G at post 6912, and which were separated (isolated) from other polynucleotides.

Thus Clark anticipates the claim.

Claim 36 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al (Nuc. Acids Res. 14(20): 7897-7914, 1986) and Clark et al (GenBank Accession No. X04500, 6/1997)

Clark (1986) teaches the sequencing of the nucleic acid sequence of SEQ ID NO:2. This procedure involved subcloning restriction fragments derived from large (12-32 kilobase) segments of genomic DNA. The subcloned fragments were then subjected to progressive exonuclease digestion to generate a set of overlapping clones which were subsequently sequenced. See page 7899, first full paragraph, and Fig. 3 on page 7902. Clark (1986) does not appear to disclose the entire sequence of SEQ ID NO:2.

Clark (1997) discloses the entire sequence of SEQ ID NO:2 and cites the Clark (1986) reference.

It would have been obvious to one of ordinary skill in the art at the time of the invention to digest the DNA sequence of Clark with restriction endonucleases such that fragments of 5000-7000 bases were produced. One would have been motivated to do so because one of ordinary skill in the art appreciates that fragments of this size are easily resolved by gel electrophoresis and are a convenient size for subcloning. The sequencing protocol of Clark involved making

progressive deletions of M13 clones comprising restriction fragments derived from genomic library sequences of 12-32 kb in length (see page 7899, first full paragraph; page 7900, first full paragraph and Fig. 1; and page 7901, line 8). M13 clones containing inserts of 5000-7000 bases would be excellent substrates for progressive deletions, and would therefore facilitate DNA sequencing. Alternatively, one would have been motivated to express any fragment of the human IL-1B gene, including one encoded by a 5000-7000 base fragment, in order to raise antibodies against IL-1β.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant argues that the claims as amended are drawn to a sequence with a C at position equivalent to 6912 of IL-1B.

Claim 34 as amended are still drawn to SEQ ID NO:2, which is the exact sequence disclosed by Clark. The sequence of SEQ ID NO:2 cannot be changed by amendment. Changes to the Sequence Listing may only be made by submission of a new Sequence Listing, and such changes must be fully supported in the Application as filed. In this case, Applicant will be allowed to file a new Sequence listing with a corrected version of SEQ ID NO:2 only if the new matter rejection outlined above can be overcome.

Claims 35 and 36 are drawn to nucleic acids which contain a cytosine at an undefined position. Specifically the cytosine is at "a position equivalent, relative to the surrounding

sequence, to position 6912". For the reasons outlined above in the rejection under 35 U.S.C. 112, second paragraph, this language fails to specify any nucleotide position. The the nucleic acid of Clark comprises a large number of cytosines, any one of which could be the cytosine of claims 35 or 36. The rejections are maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Richard Schnizer, Ph. D.